REMARKS/ARGUMENTS

Claims 95-98 and 114-132 are active in this case.

Support for the amendment to Claim 95 and newly added Claims 114-132 are found on page 10, 1st, 2nd and 3rd paragraphs; page 15, 1st ¶, and the Examples on pages 23-24. The fact that the cells so cultured have enhanced cytokine secretion is disclosed on page 11, lines 6-7 and pages 23-26.

No new matter is believed to have been added by the amendments.

The claims of this application are directed to methods of obtaining human T cells with enhanced replicative function and cytokine secretion. Those cells are cultured under certain conditions as defined in the claims. As discussed in the specification, an advantage of the present invention is the discovery that culturing cells, including T-cells, one can obtain a population of cells with enhanced replicative function and cytokine secretion making these cells particularly useful for therapeutic applications.

One feature of the invention as indicated before is the aspect where the cell density of the T-cells is not substantially reduced or adjusted at any time during the culturing while maintaining a constant culture volume. Notwithstanding what is stated in the Action and the cited US '700 patent, performing such a method in this manner for T-cells was opposite of what was conventionally done. Therefore, the fact that it worked and worked so well that the T-cells obtained had, in fact, enhanced replicative function and cytokine release was not predictable.

The sole rejection raised in the Action is an obviousness rejection citing U.S. '126 with newly cited U.S. '700. By the Office's own admission and as apparent from a careful reading of the cited art, neither publication describes or suggests the aspect of culturing T-cells. Indeed, the U.S. '126 patent is focused on culturing dendritic cells (i.e., not T-cells)

and the U.S. '700 patent provides a teachings for culturing cells, generally, in the specialized apparatus that is the subject of that patent. In fact, the only mention of cells in the U.S. '700 patent is in column 2 where the patent describes that the method and apparatus can be used to culture any cell, bacterial, human or other. Bacterial cells and mammalian cells (such as transformed cells that are commonly cultured) have vastly different properties, require vastly different culture conditions and techniques and, in fact, it is well-known that even among cells of a particular species that what one knows about one cell type gives the researcher no *a priori* information as to how a cells of a different type will behave in that culture. It is further worth noting that the U.S. '700 patent provides no working examples of actually culturing cells in its specialized apparatus, particularly not mammalian cells, nor T-cells.

Further, as explained in the previous reply supported by more relevant literature for T-cells, the conventional process of culturing is to maintain T-cell concentrations in tissue culture flasks or gas permeable culture bags at an optimum of 10^5 to 10^6 per ml or less based on common knowledge in the field of cell culture. Conventional wisdom suggests that when T-cells achieve a maximum cell concentration of 1-3 million cells per ml, the cultures must be diluted and split immediately into multiple cultures such that density is restored to 5×10^5 cells/ml or less (i.e. "hemi-depletion" to maintain low cell density by adding medium and/or splitting individual cultures into multiple cultures). Typically, this process is repeated several times (generally every 2-7 days during the course of standard T-cell culture (See Riddell and Greenberg, 1990 *J Immunol Methods 128*:189-201, previously submitted, for one representative example of this approach for T-cells).

Thus what was previously provided by the Applicants is, in fact, more relevant to the art of culturing T-cells than either of the cited U.S. '126 or U.S. '700 patents--reiterating that the teachings of those references are to dendritic cells or prophetically any cells, bacterial, yeast, mammalian, etc.

The Office cites the recent Supreme Court case in *KSR Intern. Co. v. Teleflex, Inc.*, 127 S.Ct. 1727, 1740 (2007) in support of the rejection. Applicants agree that this is the law and that is why it was cited in the Applicants previous reply. Based on that law, if known elements are combined to achieve the predictable outcome then the claim is obvious. Admittedly, culturing dendritic cells was known as evidenced by the cited US '126 patent, medium exchange without splitting cells to achieve high density cultures was prophetically described by the US '700 patent, and culturing T-cells was known (see the publications previously cited by the Applicants, one of which is Riddell and Greenberg, cited above).

That the cited art does not actually teach a method of culturing T-cells, that the actual relevant art teaches not to culture as claimed here, and that the Applicants have discovered that not only can T-cells be cultured in direct contrast to the conventional knowledge but that such cultured T-cells are better than would have been thought in such a unconventional T-cell culturing process, provides an undeniable conclusion that what the claims set forth was entirely unpredictable. Following the law of *KSR* applied to the fact that the art teaching culturing T-cells taught not to do it the way that is claimed and the Applicants discovery that when T-cells are cultured as claimed yields something more than what would have been predicted demonstrates that the claims would not have been obvious.

Simply for reference again, it should be noted that the T-cells derived in the examples proliferate more vigorously (after culture to densities exceeding 10-40 x 10^6 per ml in a single bioreactor cassette) and also release cytokines at higher levels than T-cells cultured in parallel under conventional low density (<1-3 x 10^6 T-cells per ml) using hemi-depletion methods. Thus, continuous culture under perfusion conditions does not have deleterious effects on cell division and may prevent or minimize immunological senescence. This unexpected result when considering conventional culture (as highlighted above) forms the basis of the invention consisting of continuous low to high density T-cell expansion without

subculture under medium perfusion conditions. This T-cell culture strategy and potential benefits on proliferative potential or cytokine release would not be obvious to one skilled in the art.

Accordingly, withdrawal of this rejection is requested.

Applicants also request a notice of allowance confirming the allowability of all pending claims.

Should the Examiner deem that any further action is necessary to place this application in even better form for allowance, he is encouraged to contact Applicants' undersigned representative at the below listed telephone number.

Respectfully submitted,

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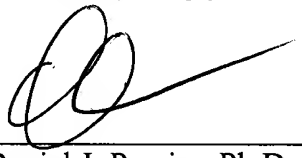

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